First Panel Session: Clinical Trial Design Considerations and Use of Multiple Drugs in Combination

Questions:

We anticipate that a number of new drugs for malaria will be studied as part of a multi-drug treatment regimen or fixed dose combination product. Data will need to be provided to demonstrate the contribution of each drug to the efficacy of the regimen/combination product. In this panel session, we would like to discuss approaches to assess the contribution of each drug to a multi-drug regimen or fixed-dose combination product.

1. Controlled human malaria infection (CHMI) studies can often assess the effect of individual drugs on short term endpoints. Please address the role of CHMI studies for the following:
    - To predict the efficacy of a new drug
    - Assessment of drug effect on later endpoints
    - Generalizability of the findings, given that CHMI studies are conducted using a single strain
    - Using results from a CHMI study to inform the design of a clinical study

2. Please comment on the feasibility of conducting a factorial design study in semi-immune adults with uncomplicated *P. falciparum* malaria to assess the added contribution of components to the overall efficacy of the regimen/combination product.

3. Please discuss relevant animal models or *in vitro* studies that would be informative to assess the contribution of a specific drug to a regimen/combination product.

4. Please discuss the role of PK/PD modeling and simulation in assessing the contribution of each component of a malaria treatment regimen based on CHMI study data.

5. Please discuss the role of PK/PD modeling and simulation in the evaluation of malaria treatments in pediatric patients and pregnant women.

Second Panel Session: Current and Emerging Technologies: Role of Parasite Detection Methods in Malaria Clinical Trials

Questions

1. Please discuss the detection method(s) to be used in CHMI studies when infected by different routes or with a different stage of the parasite, such as:
   - bites of the infected mosquitoes,
   - injected with the sporozoites intravenously, or
   - infected erythrocytes

   Please discuss the assay(s), their performance, and threshold for positive findings to identify patients that need rescue therapy.

2. Please discuss the following with regard to using molecular assays in clinical trials:
   - As a tool for enrolling subjects
   - To differentiate recrudescence from new infection and their ability to differentiate multiple strains, including those present in low density

3. What additional information should be collected besides genotyping to confirm resistance to antimalarial drugs in an endemic area?